Abstract

Microsponges are at the forefront of the rapidly developing field of novel drug delivery technology. Microsponges drug delivery technology holds a great promise for reaching the goal of controlled and site-specific drug delivery and hence, has attracted wide attention of researchers. Conventional drug delivery system often produces over or under medication result in various adverse drug reactions (ADRs) due to unpredictable drug release pattern. The microsponges based drug delivery overcome problem associate with conventional drug delivery by controlled and localized release of the active drug according to the specific need of the therapy. microsponges have various advantages over the other drug delivery system such as integrated to optimize the efficacy and cost-effectiveness of the therapy. Microsponges technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability,

Increased elegance, and enhanced formulation flexibility. In addition, numerous studies have confirmed that microsponges systems are nonirritating, nonmutagenic, non-allergenic, and non-toxic. The drawbacks associated with the existing commercial products of immediate release of drug into targeted areas, increased frequency of application also accumulation of excess amount of the drug at the targeted site it may give undesired harmful effect. so, the controlled release pattern of microsponge formulation may overcome this problem. It is unique technology for the controlled release of active agents and consists of microporous beads loaded with active agent. In the Present Project Work the main purpose to develop Microsponge based drug delivery of selected drug and it may achieve controlled drug release after evaluating formulation ultimate results to minimise the drawbacks of conventional dosage form.

Keywords: Microsponges, Controlled release, Porous microsphere, conventional dosage form

Introduction

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc. This Company developed a large number of variations of the procedures and those are applied to the cosmetic as well as over-the-counter (OTC) and prescription pharmaceutical products. Won received US patent for developing Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen (United States Patent 4,690,825)

September 8, 1992, Won R (Palo Alto, CA) of Advanced Polymer Systems, In (Redwood City, CA) received US patent for developing Two-step method for preparation of controlled release formulations (United States Patent 5,145,675) . Advanced Polymer Systems, Inc. and subsidiaries ("APS" or the "Company") is using its patented Microsponge (R) delivery systems and related proprietary technologies to enhance the safety, effectiveness and aesthetic quality of topical prescription, over-the-counter ("OTC") and personal care products like tretinoin, 5-fluorouracil and Vitamin-A etc. As on July 23, 2006, the Company has a total of 10 issued U.S. patents and an additional 92 issued foreign patents.[1]

Many of the researcher work on the microsponge formulation such as M. Jelvehgari et al (2006) developed Benzoyl peroxide microsponges for the treatment of acne and athletes foot. which was successful releasing the drug in controlled manner with minimal skin irritation [2]. Srivastava et al (2012) developing calcium-pectinate matrix tablet for colon-targeted delivery of meloxicam (MLX) microsponges.[3] Panday et al (2015) developed the microsponge technology used to facilitate the controlled release of active drug into the skin in order to reduce the systematic exposure and minimize local cutaneous reactions of active drugs. Researcher was design and evaluate the gel formation of microsponge entrapped lornoxicam to increase the effectiveness of the treatment.[4] Patel et al (2016) developed ethyl cellulose Microsponges formulation for topical delivery of fluconazole for skin fungal infection.[5] Abdellatif et al (2017) developed A novel controlled release microsponges containing Albendazole oral dosage form for treatment of parasitic worms.[6]

Nebivolol-loated microsponges system for healing of diabetic wounds was prepared by Pandit et al (2017) Tadweeet al (2018) develope Lansoprazole microsponge oral (capsule) dosage form for delayed release.[7]

The Microsponge Delivery System (MDS) is a patented polymeric system consisting of porous microspheres. They are tiny sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface through which active ingredient are released in a controlled manner. The size of the microsponge‟s ranges from 5-300μm in diameter and a typical 25μm sphere can have up to 250000 pores and providing a total pore volume of about 1ml/g for which provides large space for drug loading. The surface can be varied from 20 to 500 m^2/g and pore volume range from 0.1 to 0.3cm^3/g. This results in a large reservoir within each microsponge, which can be loaded with up to its own weight of active agent.

The scanning electron microscopy of the microsponge particle reveals that its internal structure as the “bag of marbles”. The porosity is due to the interstitial spaces between the marbles. The interstitial pores can entrap many wide range of active ingredients these entrapped microsponges may then integrated or formulated into product forms, such as creams, lotions, gel, powders, soaps, capsules and tablets etc according to suitable drug therapy.[8]

So, The microsponge based drug delivery technology have more opportunity to develop flexible novel dosage form for selected drug.

Advantages of Microsponges :[9]

1. Microsponges show acceptable stability over pH ranging from1 to 11 and at high temperatures (up to130°C).
2. Microsponges exhibit good compatibility with various vehicles and ingredients.
3. Microsponges have high entrapment efficiency.
4. Microsponges are characterized by free flowing properties.
5. The average pore size of microsponges is small, in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives.
6. Microsponges are non-allergenic, non-irritating, nonmutagenic and non-toxic.
7. Microsponges can absorb oil up to 6 times their weight without drying.
8. They have superior formulation flexibility.
9. Microsponges formulations can be cost effective
10. Extended release .
11. Improve bioavailability of same drugs.
12. Improves stability, thermal, physical and chemical stability.
13. The microsponges are free flowing and have better compressibility, thus may be effectively converted to solid oral dosage form.

Advantages over conventional formulations:[10]

Characteristics	Microsponge drug delivery	Conventional drug delivery
Drug release rate	programmable drug release	Drug release immediately
At Targeted site	Maintain the Drug concentration	Highly concentration layer of active ingredients
Efficacy	Optimize the efficacy	less efficacy
Dose frequency	It may Require less frequency of dose	Require high frequency of dose
Cost	Cost-effective	Expensive
Irritation	May Reduces irritation of drug ,non allergenic and non toxic	Causes irritation of drug
Stability	It may be more stable than conventional dosage form	Less stable

Advantages over Microencapsulation

Microsponges	Microencapsulation
Good compatibility with vehicle & ingredients	Possible cross reaction between core and material
Easy to obtain formulation	Difficulty to obtain formulation
Cost effective	More production costs

Examples of Microsponge drug delivery with their formulations

Microsponge Delivery system	Drug	Disease
Topical gel	Benzoyl peroxide Fluconazole Terbinafine HCL	Anti-Acne Treatment Inflammation Anti-fungal
Creams	Hydroquinone and retinol	Melanoma
Tablets	Indomethacin Paracetamol Dicyclomine	Inflammation Colone targeting Anticholinergic
Implants	Poly(DL-lactic-co-glycolic acid)	Skin tissue engineering

List of Marketed products based on Microsponges

Product name	Manufacturer	Pharmaceutical use
Glycolic Acid Moisturizer	AMCOL HEALTH	Anti-Wrinkles
Retin A Micro	Ortho-McNeil pharmaceutical, Inc	Acne vulgaris
Retinol cream	Biomedic	Maintain healthy skin
Carac cream 0.5%	Dermik laboratories,Inc	Actinic keratoses
EpiQuinmMicro	SkinMedica Inc	Hyper pigmentation
Budesonide (tablet)	Entocort	Management of ulcerative colitis

Review of literature

S.Salah et al (2018) : Novel Miconazole (MCZ) microsponges gel as an attractive dosage form for vaginal candidiasis. The proposed formula has the potential to minimize the local side effects of the drug due to the controlled release characteristic, which increases patient compliance. MCZ microsponges were prepared applying Quasi emulsion method. Evaluate MCZ microsponges by FTIR, DSC, XRD and SEM studies, total drug content and entrapment efficiency. The optimised MCZ microsponges were incorporated into Carbopol gel, then the viscosity and bioadhesion were examined. The in vitro antifungal activity of MCZ microsponges gel was comparable to the market product. In vivo, MCZ microsponges vaginal gel was more effective than the market product ($p < 0.05$) in eradicating Candida infection in rats.[11]

Bhatia et al (2018): The aim of the present study was to improve the release rate of curcumin by microsponges prepared through quasi-emulsion solvent diffusion technique using ethyl cellulose and PVA as carriers. The microsponges were characterized by FTIR, DSC, XRD and SEM studies, total drug content and entrapment efficiency. The prepared microsponges were further filled in hard gelatin capsule shell and then loaded in carbopol gel to evaluate its potential in oral and topical drug delivery.[12]

Tadwee et al (2018): The aim of study is to develop microsponge based delayed release dosage form, technique used to manufacture microsponge was Quasi emulsion diffusion technique. Eudragit L 100 and Eudragit S 100 polymer is used to incorporate lansoprazole in microsponge. Lansoprazole is acid labile drug hence release of lansoprazole was delayed from acid environment. Microsponge was evaluated. Optimized microsponge blended with other diluents and filled in capsules. Blend containing lansoprazole Microsponge were evaluated for SeDeM parameters to check its flow. The microsponge formulation F2 showed delayed release of lansoprazole in buffer stage pH 6.8 by passing the acidic stage. The result reveals that developed

microsponge are cost effective and can be used as a delivery system for acid labile drug lansoprazole to avoid its degradation in acidic media of the stomach.[7]

C.Rathore et al (2017) :The present research was aimed to formulate erosion based matrix tablets of ketoprofen micro-sponges for spatial-colon targeting. microsponges prepared by Quasi emulsion diffusion technique. For the optimization, the effects of independent variables like solvent volume and concentration of chitosan were studied on the mean particle size, percent entrapment efficiency (% EE) and *in vitro* drug release. Scanning Electron Microscopy (SEM) image of the micro-sponge formulation revealed that the surface of the micro-sponge was nearly spherical and porous. Optimized micro-sponge formulation was further formulated into erosion based matrix tablet and evaluated for quality control parameters. The developed MST of ketoprofen has the ability for spatial and temporal delivery, thus could be employed to treat various colonic diseases.[13]

P.Mahesh Kumar et al (2017): Silver sulfadiazine has been frequently used as an antibacterial agent for topical treatment of partial thickness burn wounds. In this study, we present the preparation of silver sulfadiazine microsponges by w/o/w emulsion solvent evaporation method. The optimized microsponge and optimized microsponge loaded gel were also evaluated.Optimized microsponge loaded gel enhanced the drug retaining capacity in the skin layers, by 3 fold higher to that of a commercial product. The antibacterial inhibitory efficiency of optimized gel was similar to the commercial product against the Staphylococcus aureus and Pseudomonas aeruginosa. Optimized gel showed reduced frequency of application, no skin irritation, low cytotoxicity on dermal cell lines and enhanced wound contraction.[14]

Dombe et al (2017) : Oxiconazole nitrate is an antifungal drug used in the treatment of fungal infection having a poor aqueous solubility, side effects and adverse reactions. The microsponge delivery system is unique technology for controlled release of active agents. The microsponges were prepared by quasi-

emulsion solvent diffusion method by using polymer eudragit S-100 and eudragit L-100. Prepared optimised microsponge and microspong gel evaluated. As compared to conventional formulation, the prepared microsponge gel are expected to remain on the skin for a longer time, gradually releasing their contents over the time. Hence, oxiconazole nitrate microsponges and microsponge gel prepared in this study are promising as being more useful than conventional formulation therapy.[15]

Patel et al (2016) : The aim of the present research was to develop Fluconazole loaded microsponge-based topical delivery system for controlled release and enhanced drug deposition in the skin. Microsponges containing fluconazole were prepared by an emulsion solvent diffusion method. The effect of formulation variables (drug: polymer ratio, internal phase volume and amount of emulsifier) and process variables (stirring time and stirring speed) on the physical characteristics of microsponges like Production yield, Mean particle size, Entrapment efficiency were investigated. The optimized microsponges were dispersed into a hydrogel and evaluated. Microsponge loaded gels demonstrated controlled release, no irritancy to rat skin and antifungal activity. An In vivo skin deposition study demonstrated four fold higher retention in the stratum corneum layer as compared with marketed cream. Microsponges-based gel formulations showed prolonged efficacy in mouse surgical wound model infected with Candida spp. Fluconazole was stable in topical formulations and showed enhanced retention in the skin indicating better potential of the delivery system for treatment of primary and secondary skin infections.[16]

Panday et al (2015) : The work involves the drug lornoxicam is a non-steroidal anti-inflammatory drug bearing analgesic, anti-inflammatory, and antipyretic property. The micro sponge technology used to facilitate the controlled release of active drug into the skin in order to reduce the systematic exposure and minimize local cutaneous reactions of active drugs. The microsponge were prepared by quasi emulsion solvent diffusion method. The internal phase consisting eudragit RS-100 and ethyl cellulose dissolved in dichloromethane and ethyl alcohol, drug is slowly added to polymer solution with continuous stirring for 4

h, and then mixture was filtered to separate the microsponges. Microsponges was characterized by parameters like scanning electron microscopy, drug content, particle size analysis, compatibility studies using differential scanning calorimetry. Microsponge-loaded gel was characterized by physical parameters of gel, measurement of PH, viscosity study, Drug content study, *in-vitro* release studies.[4]

Osmani et al (2015): The intention behind present work was to develop microsponge based novel dosage form for sustained delivery of domperidone. Quasi-emulsion solvent diffusion method was employed using Eudragit RS-100 with various drug-polymer ratios for the preparation of microsponges. Characterization techniques followed for the formed microsponges were DSC, FTIR, SEM, XRD and particle size analysis, along with morphology, drug loading and *in vitro* drug release. The microsponges were then loaded in capsules followed by *in vitro* drug release study; which depicted that microsponges with drug-polymer ratio of 1:2 were more proficient to give extended drug release of 76.38 % at the end of 8 h, superior in contrast to conventional marketed formulation. Hence, the developed microsponge based formulation of domperidone would be an expectant, promising substitute to conventional therapy of gastroparesis, emesis and alike gastric ailments.[17]

R. Srivastava et al(2012) : The work was aimed at developing calcium-pectinate matrix tablet for colon-targeted delivery of meloxicam (MLX) microsponges. Modified quassi-emulsion solvent diffusion method was used to formulate microsponges (MS).The optimized colon-targeted tablet (MS5T2) shielded MLX loaded microsponges in gastrointestinal region and selectively delivered them to colon, as visualized by vivo fluoroscopy in rabbits. The pharmacokinetic evaluation it shows calcium pectinate matrix tablet loaded with MLX microsponges was developed as a promising system for the colon-specific delivery that has potential for use as an adjuvant therapy for colorectal cancer.[3]

Objective

Aim : Design, Development and Evaluation of controlled release Microsponge Drug Delivery System.

Objective of research work :

- To Optimize and Formulate the Microsponges using selected drug and excipients etc.
- To Prepare and Evaluate the Controlled release Microsponge formulation.
- To Obtain Controlled release of drug formulation.
- To Improve efficacy and drug loading capacity.
- To Minimize the toxicity.
- To Evaluate in-vivo drug release studies on experimental animals of optimized controlled release microsponge formulation.

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Methodology to be Adopted:

1) Literature review

2) Selection and Collection of Drug & excipients

3) Characterization of Drug and excipients

4) Compatibility studies

5) Preparation of Microsponges

Method of Microsponges preparation based on Physico-chemical properties of drug to be loaded. following techniques are used for microsponge preparation. According to physico-chemical properties of drug one of the following technique may be selected for Microsponges preparation.

- Liquid-liquid suspension polymerization
- Quasi-emulsion Solvent Diffusion
- Water in Oil in Water(W/O/W) emulsion
- Oil in Oil Emulsion solvent Diffusion
- Lyophilization
- Ultrasound-assisted production.
- Addition of porogen

6) Characterization of Microsponges or Microsponges formulation.

- Production Yield, Entrapment efficiency
- Particle size analysis
- Flowability testing (Angle of repose/ Carr's indices/Hausner ratio)

- Scanning electron microscopy (SEM)
- Fourier Transform Infrared Spectroscopy (FTIR)
- X-Ray Diffraction study (PXRD)
- Differential scanning calorimetric (DSC)
- In vitro drug release studies
- In- vivo drug release studies on experimental animals.
- Stability studies

7) Statistical Analysis, Data Interpretation and Conclusions.

Chapter Scheme or method for preparation of microsponge may be altered in the view of experimental Observation.

Importance of study

Microsponge drug delivery system holds a promising opportunity in various pharmaceutical applications in the upcoming future as it has unique properties like enhanced product performance and elegancy, extended release, improved drug release profile, reduced irritation, improved physical, chemical and thermal stability which makes it flexible to develop novel product forms. The purpose of doing work on microsponge formulation, after assemble data on the present information's, current technologies and recent literatures and other contributing factors used it may achieve controlled release of active drug and minimize the drawbacks of conventional drug delivery systems. Based on the literature surveyed, it may be concluded that simple production, various innovative applications with a programmable release makes Microsponge drug delivery system unique, novel also expands its application in various drug delivery. Microsponge technology which is needed to be explored for patient compliance provides the improved efficiencies of various types of pharmacotherapies with novel product development.

International status: In the current years the development of new drugs is not sufficient for the drug treatment. But it also involves the development of suitable drug delivery system at site of action. The biggest challenge up to date is to control the delivery rate of the medicaments by various modern technologies met by extensive research. New classes drugs such as pharmaceuticals, biopharmaceuticals typically cannot be effectively delivered by conventional mean. Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system.

Most of the studies in last few years with microsponge showed a promising result and accordingly there is reported number of patents on microsponge drug delivery.

National status : The market holds lots of potential for microsponge technology and the versality they offer. Microsponge delivering system can be winning strategy for a new generation of pharmaceutical and cosmetic industry. Microsponge drug delivery have potential to overcome the challenges related to conventional dosage forms for the treatment of various diseases.

Proposed work plan

Year wise plan of work to be achieved

Sr.no	Expected target to be achieved	Tentative Time
1	Literature Survey, Selection and Collection of Drug and Excipients	July-December 2019
2	Formulation developments & Optimization	January- June 2020
3	Evaluation of Microsponges Formulation	July-December 2020
4	In vivo studies	January- June 2021
5	Statistical Analysis, Data Interpretation and conclusion /Research communication	July-December 2021
6	Research writing and Submission	January-April 2022

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